REMARKS

The Examiner's attention to this Application is greatly appreciated. Applicants respectfully acknowledge the acceptance of the RCE under 37 C.F.R. §1.114, including the fee set forth in 37 C.F.R. §1.17(e) and the withdrawal of the finality of the previous Office Action. In addition, Applicants respectfully acknowledge the following rejections have been withdrawn by the Examiner, as provided in the previous Office Action:

- the rejections against claims 34, 38 and 46 due to the cancellation of said claims;
- the rejection of claims 38, 39 and 54 under §112, first paragraph;
- the rejection of claim 40 under §112, first paragraph;
- the rejection of claims 44-46 under §112, second paragraph; and
- the rejection of claims 32, 35 41 and 54 over WO 97/02827 to Van Beek et al.

I. STATUS OF THE CLAIMS

Claims 1-31, 34, 38 and 46 were cancelled previously. Claims 47-53, and 55-57 are withdrawn. Claims 32, 33, 35-37, 39-45 and 47-62 are pending. Claims 32, 39-41, 44, 45, 54 and 58-62 are rejected. Claim 62 is amended. Claim 39 is cancelled herein. Claims 63-65 are new. Care has been taken to prevent the introduction of new matter into the claims.

Applicants do not concede in this Application that the amended claims are not patentable, as the present claim amendments are only for facilitating expeditious prosecution of the application in light of the Examiner's comments. Applicants respectfully reserve the right to pursue these and other claims in one or more continuation or divisional patent applications.

II. OBJECTIONS TO THE CLAIMS

Claim 39 is objected to under 37 C.F.R §1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. In response, Applicant has cancelled Claim 39.

III. REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

A. Claims 32, 33 35-37, 39 and 54 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement.

Applicant respectfully traverses the rejection. The specification describes the effect of NH_2-olpadronate on bones and osteoblast cells. Dose-response curves are provided. Experimental results are described comparing the activity of NH_2-olpadronate to olpadronate, a drug of known utility in treating and preventing osteopathy.

The Office Action states that "'maintaining a healthy bone structure' in a 'patient without an osteopathy' would require the patient not to develop any osteopathies. This is considered a preventive method." Applicant points out that the claims do not include a limitation that the patient fails to develop any osteopathy. The preamble language describes the purpose of the method. The body of the claim contains claim limitations. It is not required for patentability that a claimed method be practiced with 100% success in every case. If this were true, a claim directed to "a method of making fire, comprising the step of striking a match on a rough surface" would fail for being non-enabled; as everyone knows, sometimes it takes more than one try to ignite a match. Just as there is no known method of striking a match that will ignite the match 100% of the time, the rejected claims are not directed to a method that never fails.

Applicant submits that only the claim limitations as written should be considered.

The Office Action states that "The prior art does not show how to identify a patient without any bone disease, disorder or any condition effecting bones" and "The existing methodology cannot identify with certainty patients that are at risk for osteoporosis." Applicant respectfully submits that those skilled in the art of medicine art capable of diagnosing osteopathy or osteoporosis, as further discussed below in section IV. Furthermore, it is pointed out that Applicant does not claim a step of diagnosing an osteopathy or osteoporosis, and so it is not relevant whether such a step is enabled in the instant application.

As evidence that methods of diagnosing osteopathies are known, Applicant submits Exhibits A-C. These web pages all describe well-known and widely accepted methods of diagnosing osteoporosis.

The Office Action sets forth a definition of "maintaining a healthy bone structure" as follows:

> In order to maintain healthy bone structure by preventing a disease, as opposed to merely delaying or reducing its symptoms, a treatment must either render the subject completely resistant to said disease after a single treatment or a limited number of treatments, or else, when continued indefinitely, continue to completely suppress the occurrence of said disease.

Applicant is unaware of from what source the Examiner is importing these limitations into the claims. The claims are not limited to maintaining a healthy bone structure under the conditions described in the Office Action. It is both common sense and understood by those in the art that maintaining one's health does not mean one will live forever or never suffer from illness. Inevitably, the patient will pass away, as does everyone, and the bone structure of the patient will cease to be healthy. It is sadly understood that methods of maintaining health cannot assure perfect health 100% of the time. Applicant certainly claims no goal so lofty.

Several conditions exist in which osteocyte and osteoblast apoptosis is affected, for example, in the events of menopause, prolonged sedentarism, aging, consumption of corticosteroids and other immunosuppressive medications, etc.

Although the prediction as to which patient may or may not develop an osteopathy is subject to some level of uncertainty, it is known that increased osteocyte or osteoblast apoptosis creates a greater chance of developing an osteopathy. Similarly, as with any prophylactic measure, it can be anticipated with confidence that those not protected will have a greater chance of developing the disease.

One skilled in the art can arrive upon the correct dosage, as studies already performed show the activity range, so the DE_{50} which keeps osteocytes and osteoblasts healthy may be estimated. Whether such dose is within a safe range can be determined according to previous experiences with similar drugs.

For the reasons stated above, Applicant requests the Examiner reconsider the rejection. The application discloses the activity of NH_2-olpadronate in sufficient detail to allow one of ordinary skill in the art to practice the invention without undue experimentation. Applicant respectfully requests the Examiner withdraw the rejection and allow the claims.

B. Claims 32-33, 35-37, 40-45, 54, and 58-62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. It is alleged that these claims contain new matter. The Office Action states on page 13 "The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Applicant respectfully traverses the rejection.

The Office Action alleges that one skilled in the art of medicine would not understand the specification to convey that a medicament comprising NH_2-olpadronate would contain NH_2-olpadronate within a range of amounts effective for treatment or effective for the maintenance of a healthy bone structure ("a bone health promoting effective amount"). As Applicant pointed out previously, this is a matter of basic pharmacology understood by those skilled in the art. Applicant again refers the Examiner to B. G. Katzung (2001) *Basic and Clinical Pharmacology* Lange Medical Books/McGraw-Hill, New York ("Figure 3-1 illustrates a fundamental hypothesis of pharmacology, namely, that a relationship exists between a beneficial or toxic effect of a drug and the concentration of the drug.") One skilled in the art could hardly read the specification to disclose that NH_2-olpadronate can treat osteopathy and maintain a healthy bone structure without making the assumption that the drug can only do so at certain effective amounts.

For the reason stated above, Applicant respectfully requests the Examiner reconsider the rejection. One skilled in the art would understand the specification to teach the claim limitation of an "effective amount" of NH_2-olpadronate. Applicant respectfully requests the Examiner withdraw the rejection and allow the claims.

IV. REJECTION UNDER 35 U.S.C. §112 SECOND PARAGRAPH

Claims 32-33, 35-37, 39-45, 54, and 58-59 are rejected under 35 U.S.C. §112, second paragraph as failing specifically point out and distinctly claim the invention. The Examiner states two bases for this rejection. The first is stated on page 10 of the Office Action:

> Applicants recite, "said method comprising administering to a patient without an osteopathy." There are no clear cut limitations on when a patient has an osteopathy versus when they don't [sic]. Many of the bone related diseases are progressive diseases, and most can only be diagnosed after they have multiple

> symptoms. Thus, how would a skilled artisan know when a patient has an osteopathy, versus when they are without an osteopathy? How is it determined? It is not clear which ones do applicant point to as representative of "a patient without an osteopathy" [sic]? Does a patient without an osteopathy have NO clinical signs? OR, do they have some clinical signs, but are still considered "healthy" (i.e. no outward appearance of osteopathy). As such, it is not clear how one would identify a patient without osteopathy and one of skill in the art would not be able to ascertain the metes and merits of the claims herein.

Applicant notes that the claim element of "a patient without an osteopathy" is recited in Claims 32, 33, 35-37 and 39. Applicant respectfully traverses the rejection.

Those skilled in the art understand "a patient without osteopathy" to mean a subject not considered to suffer from an osteopathy by conventional diagnostic measures. Those skilled in the art understand how to diagnose an osteopathy. Applicant submits the web pages in Exhibits A-C as examples of established and well-known methods of diagnosing one osteopathy, osteoporosis. Applicant does not dispute that some osteopathies may have early stages during which they are asymptomatic or during which diagnosis may be difficult. Nearly every disease has such a stage. Nevertheless, those skilled in the art have established conventions as to what symptoms indicate the presence or absence of a given disease. Furthermore, any physician within the specialty knows how to identify the osteopathy risk factors in healthy subjects. When the disease is at a stage when a clear-cut diagnosis is difficult or impossible, physcians may rely on experience or intuition in drawing a diagnosis. It is said that medicine is partially an art and partially a science. Not every diagnosis is one hundred percent certain. Nonetheless, one skilled in the art of medicine is considered able to determine when an osteopathy is present or absent in a given case, although in some cases the physician may conclude that prophylactic action is warranted on the bases of less than 100% certainty in the diagnosis.

The second basis for the rejection for failure to comply with the written description requirement is stated on pages 10-11 of the Office Action:

> Claim 41 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim [41] recite[s] the phrase, "post-treatment of osteopathies". It is not clear whether the claim require[s] a patient to be free of osteopathies as a result of treatment of osteopathies or whether after some treatment for osteopathies is given [sic]. As such, one of skill in the art would not be able ascertain the metes and bounds of the claim herein

Applicant observes that there is no basis in the claim itself to believe that the patient is required to be free of osteopathy. However, the term "post-treatment" by definition requires that some treatment for osteopathy as previously been given. One of ordinary skill in the art would understand the meaning of the word "post treatment."

Those skilled in the art understand the term "post-treatment" to mean the time when the prescribed basic treatment ends (for example, a conventional antiresorptive bisphosphonate, calcitonins, or hormonal therapies). When the treatment ends, the disease generally progresses. Anti-resorptive treatments have no management-specified duration; sometimes they are discontinued when the disease wanes, sometimes they are risky whenever the resorption inhibition is prolonged. As a result, antiresorptive compounds are often poor post-treatment options.

NH_2-olpdronate is the first viable post-treatment option because it exerts an anabolic effect (for example, on the osteocyte/osteoblast population density) without promoting a greater metabolic depression due to resorption inhibition. This valuable property was not previously expected.

The basis for the rejection of Claim 42 is not stated, as Claim 42 recites neither "a patient without an osteopathy" nor "post-treatment of an osteopathy."

For the reasons stated above, Applicant respectfully requests the Examiner reconsider the rejection. Those of ordinary skill in the art of medicine are able to diagnose disease (including

osteopathy), and are able to understand what is meant by the word "post-treatment." There is no stated basis for the rejection of Claim 42. Applicant respectfully requests the Examiner withdraw the rejection and allow the claims.

V. REJECTIONS UNDER 35 U.S.C. §102(b)

Claims 60 and 62 are rejected under 35 U.S.C. §102(b) as being anticipated by WO 97/02827 to Van Beek et al. (herein after "Van Beek"). The Office Action states "Van Beek et. al. discloses the use of [NH_2-olpadronate] for the treatment of all forms of osteoporosis, arthritis and periodontal diseases, as well as diagnostic purposes."

Claim 62 as amended recites:

> A method according to claim 60, wherein the bone disorder is selected from the group comprising ~~osteoporosis~~, Paget's disease, ~~arthritis~~, ~~peridental osteopenia~~, adolescent scoliosis, fracture, disuse osteopenia, post-transplant osteopenia, hyper-parathyoidism-associated, metabolic bone disease, osteopenia of prematurity, and ossification disorder, or a combination thereof.

Applicant submits that the amendment to Claim 62 avoids the disclosure of Van Beek, as Van Beek teaches only the treatment of osteoporosis, arthritis, and periodontal disorders.

Claim 60 recites in part:

> A method for treatment of a bone disorder, said method comprising administering to a patient a medication comprising: (a) a bone-health promoting effective amount of 1-amino-3-(N,N-dimethylamino) – propylidene-1,1-bisphosphonic acid, any of its soluble salts or any of its hydrates...

(emphasis added). The Office Action alleges that the element of "a bone-health promoting effective amount of" NH_2-olpadronate is explicitly taught by Van Beek for the following reason:

> Example 4 and Figure 1 shows binding of bone mineral by 1-amino-3-(N,N-dimethylamino) – propylidene-1,1-bisphosphonic acid as well as olpadronate at various concnetrations. Example 5 and Figure 2 shows inhibition of calcium incorporation by 1-amino-3-(N,N-dimethylamino) – propylidene-1,1-bisphosphonic acid and similar compounds. Half maximal inhibition for 1-amino-

> 3-(N,N-dimethylamino) – propylidene-1,1-bisphosphonic acid was disclosed as $2x10^{-7}$M. (Page 11, last paragraph). Van Beek et. al. further discloses that 1-amino-3-(N,N-dimethylamino) – propylidene-1,1-bisphosphonic acid inhibited crystal growth with half maximal concentrations of $3x10^{-6}$ M. (Example 6, page 12). These concentrations are considered to fall in the claimed range of a "bone health promoting effective amount".

(emphasis added). Applicant respectfully points out that the examples to which the Examiner refers are limited to certain concentrations of NH_2-olpadronate, but not amounts. An "amount" of an ingredient in a medicament does not refer to the concentration of the ingredient in the patient after administration. Rather, it refers to the mass of the ingredient in the dosage form of the medicament itself. For example, the Examiner's attention is directed to Claim 61, which recites:

> The method of claim 60, wherein said amount is selected from the group consisting of: 0.1-1000 mg per oral administration, and 0.02-200 mg per parenteral administration.

The amount is expressed as a given mass per administration. Although a given amount of an ingredient will be related to the concentration of the ingredient within the body of the patient, many other factors will affect the ultimate concentration in various tissues. For this reason, Applicant respectfully submits that the concentrations of NH_2-olpadronate disclosed in Van Beek do not disclose an effective amount of NH_2-olpadronate in a medicament.

Applicant maintains the previously submitted argument that Van Beek merely teaches the utility of NH_2-olpadronate as a carrier for the treatment of various diseases, and not as the active ingredient.

For the reasons stated above, Applicant respectfully requests the Examiner reconsider the rejection. The cited reference does not disclose the element of an "effective amount" of NH_2-olpadronate in a medicament, and the cited reference does not disclose treatment of any of the

enumerated ills of Claim 62. Applicant respectfully requests the Examiner withdraw the rejection and allow the claims.

VI. REJECTIONS UNDER 35 U.S.C. §103(a)

Claims 40-45 and 58-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Beek in view of Brumsen et al., *Reviews in Molecular Medicine*, 76:4, 266-283 (1997) (herein after "Brumsen"). The Examiner relies on Van Beek to teach or suggest that NH_2-olpadronate is useful in the treatment of osteoporosis, periodontal disease, and arthritis. The Examiner relies on Van Beek to teach or suggest that NH_2-olpadronate is useful in the treatment of all osteopathy because NH_2-olpadronate lacks antiresorptive activity. The Examiner relies on Brumsen to teach administration of bisphosphonates (olpadronate) to children and persons over 40 years of age. The Examiner further relies on Brumsen to teach administration of bisphosphonates (olpadronate) for osteopathies generally. Applicant respectfully traverses the rejection.

A. Assuming for the sake of argument that the Office Action has established a prima facie case for obviousness, Applicant submits that rebuttal evidence of the unexpected properties of NH_2-olpadronate must be considered. Applicant has previously explained, based on the specification, that NH_2-olpadronate unexpectedly has no antiresorptive activity and has a reduced ability to induce osteocalcin synthesis and intracellular calcium influx compared to olapadronate. Applicant herein submits additional evidence of unexpected properties of NH_2-olpadronate.

Applicant respectfully calls the Examiner's attention to Exhibit D, the Abstract of the presentation of Plotkin et al. In this abstract, Plotkin describes the effects of alendronate and NH_2-olpadronate (IG9402) on mice. The mice were either implanted with placebo or with a

pellet of prednisone (prednisone is known to induce osteoporosis). Plotkin observed that both NH_2-olpadronate and alendronate prevent the apoptosis of osteoblasts and osteocytes. Both NH_2-olpadronate and alendronate prevent weakening of vertebral resistance to compression.

However, Plotkin observed unexpected differences between the two compounds. Whereas alendronate decreased the rate of cancellous bone formation, NH_2-olpadronate had no effect on bone remodeling. Whereas alendronate decreased serum levels of C-telopeptide, decreased serum levels of osteocalcin, decreased levels of osteocalcin mRNA, and decreased levels of collagen 1A1 mRNA, NH_2-olpadronate had no effect (note that Applicant has observed a low level of induction of osteocalcin synthesis by NH_2-olpadronate).

Plotkin concluded "Preservation of bone strength without inducing osteoclast apoptosis by IG9402 [NH_2-olpadronate] opens new possibilities for the treatment of bone fragility in conditions in which a decrease in bone remodeling is undesirable."

Applicant respectfully requests the Examiner reconsider the rejections in light of this rebuttal evidence. NH_2-olpadronate is thus revealed to possess numerous properties that would not have been expected merely from its chemical similarity to olpadronate and alendronate. Applicant submits that this evidence of unexpected properties renders the claims non-obvious, and is sufficient to rebut any prima facie case of obviousness that might have been established in the Office Action. Applicant thus respectfully requests the Examiner withdraw the rejections and allow the claims.

B. In response to Applicant's previous argument that there is no motivation to combine the references, because Brumsen teaches against the use of compounds lacking the critical property of antiresorptive activity, the Examiner states "However, the court in KSR v. Teleflex foreclosed the argument that a specific teaching suggestion or motivation is required to

support a finding of obviousness. (See the recent Board decision Ex Parte Smith, Bd. Pat. App. & Interf. June 25, 2007; Citing KSR v. Teleflex, 82 USPQ2d at 1396)."

Applicant respectfully points out that the Examiner has misunderstood *Ex parte Smith* and *KSR v. Teleflex*. Neither decision has overturned the requirement for some showing of a motivation to combine references to make a prima facie case of obviousness, as established by the Supreme Court in *Graham v. John Deere Co.*, 383 U.S. 1, 12 (1966). The holding of *KSR v. Teleflex* is more completely described on page 14 of *Smith*:

> The Court explained, "[o]ften, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." Id. at 1740-41, 82 USPQ2d at 1396. The Court noted that "[t]o facilitate review, this analysis should be made explicit." Id., citing In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness"). However, "the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." Id.

There remains a requirement that an explicit reason to combine the references be shown.

Applicant again reminds the Examiner that Brumsen teaches that a different bisphosphonate than claimed (olpadronate) is useful for treating osteopathies as a result of its antiresorptive properties. Van Beek teaches that NH_2-olpadronate is useful as a result of its complete lack of antiresorptive properties. One would not read Brumsen to suggest that a structurally related compound that lacks antiresorptive properties (taught by Brumsen to be critical) would be useful for the same purposes as the highly antiresorptive compound olpadronate.

KSR v. Teleflex has not overturned the doctrine that a teaching away in the cited references tends to rebut the obviousness of the combination of references. A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984) (see MPEP 2141.02, 8th Edition, issued after *KSR v. Teleflex* and after *Ex parte Smith*).

The justification for combining the references is explained on page 18: "One of ordinary skill in the art would have reasonably expected that the use of [NH_2-olpadronate] as claimed herein would be successful because Beek et. al. showed in comparison with olpadronate, the compound of the instant application has similar or better effects." Applicant respectfully points out that Van Beek's results do not necessarily indicate that NH_2-olpadronate has "better effects" than does olpadronate.

Van Beek teaches that NH_2-olpadronate binds to bone mineral in a similar fashion to olpadronate (Fig. 1 of Van Beek); that NH_2-olpadronate inhibits calcium incorporation into bone devoid of osteoclast cells in a similar fashion to olpadronate (Fig. 2 of Van Beek); that NH_2-olpadronate inhibits the growth of calcium oxalate monohydrate crystals in a similar fashion to olpadronate (Example 6 of Van Beek); and that NH_2-olpadronate has much less antiresorptive activity than does olpadronate. Binding to bone mineral and inhibition of calcium absorption into bone are not properties which themselves indicate a compound is useful in treating osteopathy. It was not until the discoveries described in the instant application that NH_2-OPD has a positive effect on osteocalcin synthesis and cytosolic calcium concentrations that the potential for NH_2-OPD to treat and prevent osteopathy became clear. Applicant emphasizes that previously antiresorptive activity was considered a desirable property in the treatment of bone

disease; most notably, antiresorptive compounds have been used with success in treating and preventing osteoporosis.

Because Van Beek observed NH_2-olpadronate to bind to bone and bone mineral, but lack antiresorptive activity, Van Beek concluded that NH_2-olpadronate would be a useful carrier for antiresorptive compounds. The carrier will migrate to the bones with the active ingredient, yet not increase antiresorption beyond the level achieved by the active ingredient. The absence of antiresorptive activity alone is no indication that osteopathy can be treated or prevented with NH_2-OPD.

Furthermore, Application points out that NH_2-olpadronate differs from olpadronate in that one compound is in the *cis* conformation, and the other in the *trans* conformation. The transformation from *cis* to *trans* is known to potentially completely change the properties molecule. For example, the analgesic opioids have given rise to antitussives with similar structures, but without narcotic effects.

For the reasons stated above, Applicant respectfully requests the Examiner reconsider the rejection. It would not have been obvious to use NH_2-OPD as described by Van Beek for the purposes described by Brumsen. Applicant respectfully requests the Examiner withdraw the rejection and allow the claims.

CONCLUDING REMARKS

For the reasons stated above, Applicant submits that the claims are patentably distinct from the prior art. Applicant submits that all claims are in condition for allowance. As such, the Applicant respectfully requests that all rejections be withdrawn, all claims allowed, and the Application passed to issue.

Applicant believes this Response and Amendment to be filed timely. Authorization is given to the Commissioner to charge fees for the addition of three excess claims, charge any other fees dues with the filing of this paper, and credit any overpayments to Deposit Account No. 50-0951.

The Applicants are grateful for the Examiner's consideration of this matter. In light of the remarks above, the Applicants respectfully request the Amendments be entered, all rejections be withdrawn, and all claims be allowed. If the Examiner still has concerns as to the allowability of any claims, he is urged to telephonically contact the undersigned at the number below.

Respectfully submitted,

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